REMARKS

Claims 1-3, 6, 13, and 14 are pending in the application. No claim amendments have been made at this time.

Claim Rejections -- 35 U.S.C. § 112

There is a single remaining rejection in this case. Claims 1-3, 6, 13 and 14 stand rejected under 35 U.S.C. § 112, first paragraph.

The Examiner has indicated that the claimed invention "was not described in the specification in such a way as to enable on skilled in the art to which it pertains, or with which is it most nearly connected to make and/or use the invention. (Final Office Action at pages 2-3). According to the Examiner, because "the only utility asserted in the specification for the claimed method is to produce a therapeutic effect[,]...the specification must provide adequate guidance to enable one of skill in the art to achieve the asserted utility. The specification asserts no utility for non-therapeutic transplantation." (Final Office Action at page 4). Moreover, the Examiner has also indicated that the pending claims are not enabled on the ground that "[g]iven the unpredictability in the art of therapeutic transplantation, the development of therapeutic protocols requires substantial experimentation. In view of the limited guidance, this substantial experimentation rises to the level of undue experimentation." (Final Office Action at page 4). Thus, the Examiner concludes that because of the unpredictability of the art of therapeutic transplantation, one skilled in the art would not be able to practice the claimed invention without undue experimentation. (*See* Final Office Action at page 4). Applicant disagrees.

Standard for Enablement

The enablement standard does not require a demonstration that the claimed invention produces a therapeutic benefit. Rather, the "how to use" requirement of 35 U.S.C. §112, first paragraph is satisfied if "the specification contains within it a connotation of how to use and/or the art recognizes that standard modes of administration are known and contemplated" M.P.E.P. §2164.01(c).

Here, the Examiner alleges that the specification teaches that the only use for the claimed methods is to produce a therapeutic effect in the host (*see*, Final Office Action at page 4).

However, Applicant notes that the instant claims do not recite any requirement for providing a therapeutic benefit to a host. Rather, the claims recite methods of transplanting one or more deposits of about 500,000 cells grown as neurospheres, which contain mitogenic growth factor-responsive neural stem cells capable of differentiating into neurons, oligodendrocytes, and astrocytes by administering the cells to a first area of the brain and infusing a mitogenic growth factor at a second area of the brain, wherein the transplanted cells retain their responsiveness to the growth factor *in vivo* and migrate from the first area toward the second area. Thus, these claims recite a process by which the cells are manipulated following transplantation. (*See*, specification at page 16, lines 6-11).

As such, contrary to the Examiner's contention, Applicant submits that the specification teaches both non-therapeutic and therapeutic uses for transplanting these cells. Either use alone is sufficient to meet the enablement requirement.

In the Amendment and Response to the August 9, 2006 Final Office Action filed on February 7, 2007 (the "February 7, 2007 Response"), Applicant submitted evidence that the neurospheres recited in the claimed methods are presently involved in Phase I human clinical trials for the treatment of lysosomal storage disorders. However, in the Advisory Action, the Examiner asserted that "Applicants arguments [in response to the Final Office Action] are not commensurate in scope with the claims because the claims broadly encompass the treatment of any disease or disorder by the instantly claimed transplantation method, whereas the evidence submitted is limited to the treatment of neuronal ceroid lipofuscinosis. Moreover, the method to be used in the Phase I trial appears to be distinct from the instantly claimed method, which requires infusion of a mitogenic growth factor in addition to transplantation of cells....Thus, there is no evidence that the method approved by the FDA for Phase I clinical trail for treatment of neuronal ceroid lipofuscinosis was developed from the teachings of the instant specification using nothing more than routine experimentation." (Advisory Action page 2).

The standard for enablement does not require human clinical trials. Nevertheless, Applicant has provided evidence that the neurospheres used in the claimed methods are currently being used in a Phase I clinical trail in human. Despite this, the Examiner has discounted this evidence by contending, among other things, that the specification does not provide specific guidance for treating neuronal ceroid lipfuscinosis (NCL). In response, Applicant notes that the

instant specification teaches that "[t]he cells and methods of this invention may be useful in the treatment of various neurodegenerative diseases and other disorders. It is contemplated that the cells will replace diseased, damaged, or lost tissue in the host. Alternatively, the transplanted tissue may augment the function of the endogenous affected host tissue" (*See*, specification at page 16, lines 22-25).

Those skilled in the art will recognize that NCL (commonly referred to as Batten's disease) is a neurodegenerative condition characterized by neuronal and glial cell death resulting from insufficient production of the secreted enzymes palmitoyl protein thioesterase 1 (PPT1) and/or tripeptidyl peptidase 1 (TPP-1). Based on results observed in mice, the neurospheres being transplanted as part of the Phase I trial are expected to reduce cell death and replace lost cells in patients suffering from NCL (*See*, Basu et al. Brain Transplantation of Human Neural Stem Cells in a Mouse Model of Batten's Disease. SFN abs. Nov.10, 2003).

As such, Applicant contends that NCL is one specific example of a neurodegenerative disease that can be treated using the cells and methods of the instant invention. Thus, Applicant contends that this clinical trail is further evidence that the methods of the instant invention are enabled.

In any event, lack of enablement is found only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. (*See,* In re Wands, 858 F.2d 731, 737 (Fed Cir. 1988) and M.P.E.P. § 2164.01 (c).) Here, Applicant submits that this standard is met.

As set forth in In re Wands, the factors used to determine whether experimentation is undue include, but are not limited to the following: (1) the breadth of the claims; (2) the nature of the invention; (3) the amount of direction provided by the inventor; (4) the existence of working examples; (5) the level of one of ordinary skill in the art ; (6) the level of predictability in the art; (7) the state of the prior art; and (8) the quantity of experimentation needed to make or use the invention base on the content of the disclosure. These factors must all be considered together and no single factor can outweigh the others.

As demonstrated in detail below, consideration of each of the Wands factors leads to the conclusion that the skilled artisan would be able to practice the claimed methods without undue experimentation.

Breadth of the Claims and the Nature of the Invention

Contrary to the Examiner's contention, Applicant notes that the instant claims recite methods of transplanting cells grown as neurospheres rather than methods of treatment or methods of therapy. Rather, the claims are directed to methods of transplanting one or more deposits of about 500,000 cells grown as neurospheres, containing mitogenic growth factor-responsive neural stem cells. Specifically, the cells are administered to a first area of the brain wherein, following infusion of a mitogenic growth factor at a second area of the brain, the cells migrate from the first area towards the second area.

Teaching of the Specification and Working Examples

The instant specification provides ample guidance (including several working examples) demonstrating how to practice the claimed methods. For example, the specification at page 14, lines 21-27 describes how *in vivo* migration of the claimed cells can be induced by following each of the steps recited in claim 1.

In addition, the specification also describes how to select and culture the cells (*see, e.g.* page 6, line 22 through page 8, line 22; page 15, lines 4-10; Example 1 at page 18, lines 10-27; Example 2 at page 18 line 28 through page 20, line 3); how to transplant the cells into a first locus of the brain (*see, e.g.* page 13, line 12 through page 14, line 3; page 15, lines 12-14; and Example 8 at page 25, lines 7-19); as well as how to induce migration of the transplanted cells away from the graft core toward the source of a mitogenic growth factor (*see, e.g.* page 15, line 14 through page 16, line 14; page 17, line 29 through page 18, line 4; Example 9 at page 25, line 20 through page 26, line 11; and Example 15 at page 30, line 3, through page 35, line 27).

Moreover, the instant specification also contains several working examples (*e.g.* Examples 8, 9, and 15), which provide the ordinarily skilled artisan with explicit guidance regarding how to perform each of the specific steps of the claimed methods of transplanting cells grown as neurospheres.

Thus, Applicant contends that the specification taken as a whole provides ample guidance regarding how to transplant cells in accordance with the claimed methods without undue experimentation.

Level of Skill in the Art and Predictability in the Art

The level of skill in the relevant art is high. As such, Applicant contends that a skilled artisan armed with the disclosure provided by the specification would have little or no difficulty practicing the claimed methods. Moreover, the level of predictability in the art is also high.

As a result, Applicant submits that the quantity of experimentation required to make and use the claimed method in view of the teachings provided in the specification as well as the level of skill in the art is merely routine.

Several recently published, peer-reviewed articles highlight this high level of skill and predictability in the art. In addition, although it is not a requirement for enablement of the claimed methods, these references also demonstrate that use of the claimed methods does produce a therapeutic benefit.

For instance, Kim et al. have shown that, when human neural stem cells (NSCs) of the HB1.F3 line are "implanted into the brain of murine models of lysosomal storage diseases, stroke, Parkinson's Disease, Huntington disease or stroke, implanted F3 NSCs were found to migrate to the lesion sites, differentiate into neurons and glial cells, and restore functional deficits found in these neurological disorders." (*See*, Kim, Brain Dev 29(4):193-201, (2007) courtesy copy enclosed; *see also,* Lee et al. Stem Cells 25(5):1204-12, (2007) for another specific example using a stroke model, courtesy copy enclosed).

Similarly, Redmond et al. report that "undifferentiated human neural stem cells (hNSCs) implanted into 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-treated Parkinsonian primates survived, migrated, and had a functional impact as assessed quantitatively by behavioral improvement in this DA-deficient model, in which Parkinsonian signs directly correlate to reduced DA levels." (*See*, Redmond et al. PNAS 104(29): 12175-12180, (2007) courtesy copy enclosed).

Additional neural stem cell transplant experiments that are closely related to the above-referenced studies were recently reviewed by Goldman and Windrem, Phil.Trans.R. Soc. B. 361: 1463-1475, (2006) (courtesy copy enclosed).

Each of these references describes the transplantation of the same cells (grown as neurospheres) that are being transplanted in the claimed methods. Moreover, in each reference, the transplanted cells survived and migrated following transplantation. Likewise, the transplant

recipient showed an amelioration of symptoms (i.e. a therapeutic benefit) following transplantation. Therefore, Applicant contends that these references demonstrate that the claimed methods do, indeed, provide a therapeutic benefit to the host.

In addition, another recent publication showed that transplanted human neural stem cells that are first labeled with superparamagnetic iron oxide can be visualized *in vivo* by magnetic resonance imaging. (*See*, Guzman et al. PNAS. 104(24): 10211-10216 (2007), courtesy copy enclosed). In this reference, the transplanted cells were shown to migrate to sites of injury within the newborn and adult rodent brain following transplantation.

State of the Prior Art

In addition to the guidance provided by the instant specification, the evidence of Phase I trials involving the same neurospheres recited in the claimed methods, and the references cited herein which provide a context for the level of expertise in the art (as well as those references already made of record), Applicant also notes that skilled medical practitioners had routinely carried out neural cell and neural tissue transplantation as of the filing date of the instant application. Specifically, Neural Grafting in the Mammalian CNS, Björklund and Stenevi, eds., Ch. 3 pp. 23-30; Ch.4, pp.31-40; Ch. 5, pp. 41-49; Ch. 6, pp. 51-59; Ch. 7, pp.61-69; and Ch. 8, pp. 71-77 (1985) (courtesy copies enclosed), which was available as of the earliest priorty date of the instant application, provides detailed guidance relating to transplantation of cells into the central nervous system, *e.g.*, parenchymally, into the ventricular cavities or subdurally onto the surface of a host brain.

Thus, Applicant submits that, as of the filing date of the instant application, neural cell transplantation was routinely achieved by those skilled in the art.

Quantity of Experimentation

The claimed methods of transplantation describe two specific straightforward steps which can easily be performed by a skilled artisan in light of the extensive guidance provided by the disclosure as well as the high level of skill in the art. Specifically, the skilled artisan would easily be able to isolate, select, and culture neurospheres containing mitogenic growth factor-responsive neural stem cells capable of differentiating into neurons, oligodendrocytes, or

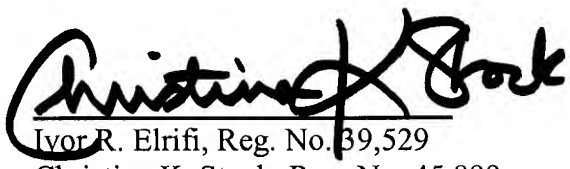
astrocytes. Moreover, one or more deposits of about 500,000 grown as neurospheres could easily be administered to a first area of the brain (*see*, claim 1(a)). Likewise, those skilled in the art would also be able to infuse a mitogenic growth factor at a second area of the brain (*see*, claim 1(b)), such that the transplanted neural stem cells retain their responsiveness to the growth factor *in vivo* and migrate from the first area toward the second area. Thus, only routine experimentation would be required by the skilled artisan in order to practice the claimed invention.

When considered together as a whole, Applicant submits that these Wands factors support the conclusion that those skilled in the art would be able to practice the claimed methods without undue experimentation. Therefore, these claims are enabled. As such, Applicant requests reconsideration and withdrawal of the only remaining rejection in this case.

CONCLUSION

Applicant submits that this paper is fully responsive and that the application is in condition for allowance. Such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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